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REPORT NUMBER 1

SCINTIGRAPHY FOR PULMONARY CAPILLARY PROTEIN LEAK

Annual Summary Report

Harvey J. Sugerman, M.D., James L. Tatum, M.D.
Jerry I. Hirsch, Pharm.D., and Alfred M. Strash, Ph.D.

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Medical College of Virginia
Richmond, Virginia 23298

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Pulmonary gamma scintigraphy is a rapid, non-invasive technique for measuring a pulmonary capillary protein leak in ARDS. In these studies, the method demonstrated that the acute anesthetized lung lymph fistula sheep model was associated with a significant pulmonary capillary protein leak. No leak was demonstrated in dogs following either large doses of Intralipid, sodium morrhuate or endotoxin. The protein leak following oleic acid could not be prevented with methylprednisolone (30 mg/kg), ibuprofen (12.5 mg/kg) MK-447 (4 mg/kg), or calcium gluconate (140 mg/kg). A significant and

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persistent leak followed the instillation of 0.1 hydrochloric acid into the trachea of dogs. Additional studies relating to these issues are in progress.

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SUMMARY

Computerized scintigraphy, employing the gamma camera, has been used in this contract to study the dynamics of the pulmonary capillary membrane leak of ^{99m}Technetium-tagged human serum albumin (Tc-HSA). In preliminary canine studies, the severity of an oleic acid-induced albumin leak was proportional to the slope of lung:heart radioactivity ratio and was more sensitive than arterial blood gases or standard chest roentgenograms. We have called this rising ratio the "slope of injury" or "slope index" (SI). Our first studies were to compare this technique to the sheep lung lymph fistula endotoxin model. Following cannulation of the right thoracic caudal efferent lymph duct, we noted that these animals had evidence of a "slope of injury" prior to the administration of endotoxin. In order to determine whether the acute sheep model developed evidence of pulmonary injury, we compared sheep with thoracotomy, retraction of the lung and lymphatic cannulation to sheep that had undergone thoracotomy only. These data demonstrated a significantly higher "slope of injury" ($p<0.01$) following thoractomy, lung retraction and lymph duct cannulation. Further studies are required in animals undergoing thoracotomy only. This suggests that the acute sheep lung lymph model is associated with acute pulmonary injury and, therefore, will make subsequent manipulation of the model difficult to interpret. In the first nine months of this contract, we have also studied a number of agents in an attempt to prevent oleic acid-induced pulmonary microvascular injury. Following a series of five control dogs, five dogs each were studied with each of the following agents: methylprednisolone (30 mg/kg), ibuprofen (12 mg/kg), the superoxide radical scavenger, WK-447 (4 mg/kg), and, in three dogs, calcium gluconate (140 mg/kg). Each of these agents was given five minutes prior to administration of oleic acid (0.05 ml/kg). None of these

agents was able to alter the rise in lung:heart radioactivity ratio following oleic acid injury. In another study, we have administered 0.1N hydrochloric acid, 2 ml/kg, into the trachea of dogs in the right lateral decubitus position and have found an acute and reproducible "slope of injury" similar to that seen with 0.05 ml/kg oleic acid. Further studies are planned to study the effects of various drugs in the acid aspiration model. Clinical experience has suggested that a few patients with bleeding esophageal varices treated by endoscopic sclerosis with sodium morrhuate develop ARDS. Sodium morrhuate is a 5% mixture of several fatty acid salts. The ARDS in these patients could either be secondary to aspiration of gastric contents or fatty acid injury. Three dogs were given 5 ml and 2 dogs 20 ml of sodium morrhuate i.v. In no instance did a significant SI occur. Intralipid administration and hyperlipidemia have been incriminated as possible causes of ARDS in man. Four dogs were given 500 ml of 20% intralipid. Although pulmonary artery hypertension and grossly lipemic serum were seen, no animal developed scintigraphic evidence of a pulmonary capillary protein leak. Six dogs were given 2.5 mg/kg endotoxin i.v. and, again, no scintigraphic evidence of pulmonary microvascular injury was seen. A number of dog and sheep were found to have evidence of a "slope of injury" during the control period prior to experimental manipulation. This suggests that some of the animals may have had a primary pulmonary disease, such as viral pneumonia, prior to their scintigraphic studies. We are now planning to analyze the initial "control" data and, should the slope be positive, the experiment will be aborted, the animal sacrificed, and the lung examined grossly and histologically for evidence of disease. Two sheep have had this occur and both gross and microscopic examination confirmed evidence of pulmonary disease. Further studies are planned to investigate endotoxin and bacterial induced ARDS in the sheep as well as oleic acid ARDS and hydrochloric acid aspiration in the dog.

FOREWORD

In conducting the research described in this report, the investigators adhere to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. NIH 78-23, Rev. 1978).

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A. Problem

The acute respiratory distress Syndrome (ARDS) is an ill-defined disorder with multiple etiologies which usually requires mechanical ventilation. Combat soldiers acquire this disorder from direct lung contusion, burn inhalation injury, inhalation of toxic substances, aspiration, multiple transfusions, as a complication of sepsis, etc. The National Heart, Lung and Blood Institute, Division of Lung Diseases, Task Force on Research in Respiratory Diseases estimated that 150,000 cases occur each year (1). Many of these are young, previously healthy persons. The overall mortality is impossible to assess, but must be quite high. Ninety-one percent of the 90 patients enrolled in the Extra-Corporeal Membrane Oxygenatory study (ECMO), most of whom probably had ARDS, died (1). Data from the nine centers participating in the ECMO study showed that more than 75% of the 600 patients receiving inspired oxygen concentration (FiO_2) greater than 50% died (1). From 1973 to 1976, 119 patients were admitted to the Respiratory and Surgical Intensive Care Units of San Francisco General Hospital with a diagnosis of ARDS (7% of all their intensive care unit admissions) and of these, 53% died (1). Although the majority of these deaths were not solely due to respiratory failure, this probably affected their morbidity and mortality.

B. Background

The initial pathophysiologic event in ARDS is thought to be a leak in the pulmonary capillary membrane. This leads to an increase in pulmonary interstitial water and protein which is then removed by the pulmonary lymphatics. If the leak exceeds the lymphatic capacity, which can increase flow by a factor of 20, pulmonary interstitial edema occurs. When the interstitial compartment reaches a critical volume and pressure, the alveolar space abruptly fills.

This causes an inhibition, or wash-out, of surfactant, which will produce alveolar collapse and a reduced FRC.• A ventilation-perfusion (V/Q) mismatch develops, with right-to-left pulmonary shunting and arterial hypoxemia.

There is a critical need for an accurate, sensitive, reproducible and non-invasive technique to measure the severity and duration of pulmonary capillary leakage in patients with ARDS. This will permit improvement in both the early diagnosis of this pathological condition as well as the objective evaluation of therapeutic interventions.

Attempts to document and quantitate the leakage of water and protein through the pulmonary capillary membrane have been fraught with frustration. Previous studies have been directed at attempts to measure pulmonary extravascular lung water (EVLW) using isotopic indicator dilution techniques. This methodology, based on studies by Chinard and Enns (2) has been shown by Korsgren et al. (3) and Marshall et al. (4) to be inaccurate, since it is flow dependent. A thermodilution-indocyanine green dye technique has also been applied to measure EVLW (5,6). This method does not appear to be as sensitive to changes in cardiac output as the isotopic indicator dilution techniques (7,8). The method provides a static estimate of extravascular lung water and would have to be repeated frequently to determine the dynamics of the leak. Brigham et al. (9) have developed a technique requiring the measurement of concentration-time curves for four radioactive agents (^{51}Cr-erythrocytes, ^{125}I-albumin, ^{14}C-urea, and ^{3}H-water) from which the extravascular lung water and the ^{14}C-urea permeability-surface area product is calculated. This technique would also provide a static estimate of extravascular lung water, seems cumbersome to use, and would also be affected by alterations in pulmonary vascular recruitment. Using a gamma probe technique, Gorin et al. (10) demonstrated a leakage of

^{113m}Indium transferrin from the chest of sheep following the intravenous injection of Pseudomonas aeruginosa bacteria. The intensity of radioactive counts correlated with the directly measured accumulation of this isotope in lung lymph. The position and aim of the gamma probe would have to be unaltered for the technique to be reproducible. It requires gamma well-counter analysis of serum samples which may limit widespread clinical utilization.

Gamma Scintillation Camera Technique: In studies from our laboratory, the computerized gamma camera was able to record and quantitate the pulmonary capillary membrane leak of ^{99m}technetium-tagged human serum albumin (Tc-HSA) in dogs following intravenous oleic acid (11,12). This technique compares the change in radioactivity over the lung to that over the heart with the construction of a lung:heart radioactivity ratio.

Radioactive Tc-HSA distributes within the whole body blood pool after intravenous injection and remains essentially within the vascular compartment. Its distribution within the body can be imaged with the gamma camera. Using the computerized gamma camera, data are collected at one second intervals for 60 seconds and then at one-minute intervals for the duration of the study. During the initial pass of the radiopharmaceutical, it is possible to define the lungs and the heart anatomically for subsequent computer analysis and construction of lung:heart radioactivity ratios. This ratio remains constant unless a pulmonary microvascular membrane injury is present when a rising ratio is present. We have called this rising ratio the "slope of injury" or "slope index" (SI).

In previous canine oleic acid studies, we have found that the SI was proportional to the severity of injury and was more sensitive than either arterial blood gas analysis or standard chest roentgenograms (12). Using this

method in the oleic acid model, it was found that the leak of Tc-HSA was much greater than the leak of ^{99m}Tc-tagged RBC's (13), that PEEP did not alter the rate of pulmonary capillary protein leak (14), that altered pulmonary vascular recruitment did not produce a rising radioactivity ratio following hemodynamic equilibration (15) and that multiple doses of Tc-HSA were associated with reproducible SI's over six hours following oleic acid administration (16). The method is noninvasive and has been used clinically to determine the severity and duration of non-cardiogenic pulmonary edema (17).

C. Approach to the Problem

The animals were anesthetized, intubated and placed beneath a Pho-Gamma IV scintillation camera fitted with a low energy, parallel hole collimator. Data were collected on "floppy disc" using a DEC mobile gamma acquisition system and transferred to a DEC medical computer for the determinations of regions of interest. Data were collected at one frame per second for 60 seconds following the Tc-HSA and then at one frame per minute for the duration of the study. Lung:heart radioactivity ratios were performed on a Xerox Sigma-5 computer. SI's were calculated from 15 to 45 minutes following administration of Tc-HSA. Animals subsequently found to have a significant SI during the control period were presumed to have a primary pulmonary illness (i.e., viral pneumonia) and were deleted from the study group. In the future we plan to test this hypothesis by analyzing the control SI prior to experimental manipulation and, should it be positive, the experiment will be stopped and the lungs removed for gross and histological examination. This has proven to be the case in two sheep recently studied. Intravascular pressures were measured with a Brush-Gould, Model 2400, 4-channel recorder utilizing a Statham strain-gauge transducer. Cardiac outputs were measured with a Kim-Ray, Model 3500 E thermodilution cardiac output computer.

1. Sheep Studies

Computerized gamma scintigraphy has compared favorably to wet to dry lung weight ratios, alveolar epithelial membrane permeability, canine lymph flow, standard radiography and light microscopy for the measurement of pulmonary microvascular permeability to albumin. The effects of altered pulmonary vascular recruitment and positive end-expiratory pressure on the scintigraphic lung:heart radioactivity have also been studied. Currently, measurement of volume and protein concentration of lymph from the right caudal efferent lymph duct of sheep is the accepted model for the study of pulmonary permeability edema (18). It is, therefore, necessary to compare our scintigraphic technique to this model. We believed that an increased pulmonary microvascular permeability, associated with an increased lung lymph flow and protein concentration would be accurately detected by alterations in the scintigraphic "slope index." In addition, it should be possible to quantitate the amount of technetium-tagged albumin appearing in the lung lymph using a "well" counter. Several attempts were made to scan awake sheep suspended beneath the gamma camera in the upright position. However, the sheep could not be kept immobilized nor were posterior images adequate for accurate lung:heart radioactivity ratios. Therefore, the sheep were anesthetized, intubated, and placed in the supine position for anterior imaging; and ventilated at a tidal volume of 20 ml/kg with 50% O_2 and 5 cm PEEP.

Initially, the sheep were subjected to thoractomy and right caudal thoracic lymph duct cannulation shortly before scanning and administration of endotoxin, the first pertubation we planned to investigate. However, sheep had very high SI's during the "control" period (see Results). These data led us to hypothesize that the "acute" lung lymph sheep model was associated with significant

pulmonary injury, which would make it difficult to interpret a pertubation such as endotoxin. We, therefore, elected to scan five anesthetized sheep for one hour following 10 mCi Tc-HSA, perform a thoracotomy and right caudal thoracic lymphatic duct cannulation (which is associated with retraction of the right lung for 30 to 60 minutes) close the chest and re-expand the lung, inject another 10 mCi Tc-HSA and scan again for one hour. These results would be compared to a group of five sheep who would be scanned before and after thoracotomy only, without lung retraction or lymph duct cannulation.

2. Canine Studies

Dogs weighing approximately 20 kg, were anesthetized with 30 mg/kg sodium pentobarbital, intubated, and ventilated at a tidal volume of 20 ml/kg with 50% O_2 and 5 cm H_2O positive end-expiratory pressure (PEEP).

a. Oleic Acid Injury: This model was chosen because of our extensive previous experience with it as well as the possible relationship of ARDS to free fatty acids in pancreatitis and the traumatic pulmonary fat embolism syndrome. We attempted to block the rising SI seen with oleic acid pulmonary microvascular injury with the following agents administered to five dogs each five minutes prior to 0.05 ml/kg oleic acid: methylprednisolone (30 ml/kg), the non-steroidal anti-inflammatory prostaglandin blocker, ibuprofen (12 mg/kg), the superoxide radical scavenger, MK-447 (4 mg/kg), and calcium gluconate (140 mg/kg). If any agent proved effective, we planned to administer it at various time intervals following oleic acid. However, no agent was found to reduce the rising SI after oleic acid.

b. Sodium Morrhuate (NaMor): A few patients with bleeding esophageal varices treated by endoscopic variceal sclerosis with sodium morrhuate have developed ARDS. NaMor is a 5% mixture of several fatty acid salts (8% palmitate, 12% palmitic oleate, 1% stearate, 2% oleate, 28% linoleate, 15%

archidate, 8% arachidonate, and 26% other). ARDS in these patients could either be secondary to aspiration of gastric contents and blood, not unusual in a cirrhotic patient with reduced mental function, or fatty acid injury. Three dogs, weighing approximately 20 kg, were given 5 ml and 2 dogs 20 ml of NaMor intravenously one hour after 10 mCi Tc-HSA. Second and third doses of 10 mCi Tc-HSA were given one and three hours, respectively, after NaMor.

c. Intralipid: This solution of neutral fat has been used in association with total parenteral nutrition and has been incriminated as a possible cause of ARDS in critically ill patients (19). Hyperlipidemia has also been implicated in ARDS associated with acute pancreatitis (20). To investigate this possibility in our dog model, four dogs were given 500 ml of 20% intralipid over 15 minutes one hour after 10 mCi Tc-HSA. This equals 100 grams of neutral fat, a very large dose. Pulmonary arterial pressure (PAP), pulmonary capillary wedge pressures (PCWP), and systemic arterial pressure (SAP) were monitored throughout the study. Cardiac outputs were measured every 15 minutes. The animals were scanned continuously beneath the gamma camera. A second and third dose of 10 mCi Tc-HSA were given two and four hours after intralipid, respectively.

d. HCl: Aspiration of gastric contents is a known complication of traumatized individuals as well as a well-recognized postoperative complication. In this study, eight dogs were anesthetized with sodium pentobarbital, intubated, ventilated at a tidal volume of 20 ml/kg, and placed beneath a computerized gamma camera. Two ml/kg 1N HCl was nebulized into the trachea of six dogs one hour after 10 mCi Tc-HSA. Second and third doses of 10 mCi Tc-HSA were given one hour and three hours after HCl, respectively. In two dogs, 0.1 N HCl was instilled and the dogs placed in the right lateral decubitus position one hour after 10 mCi Tc-HSA. The animals were given a second dose of Tc-HSA

10 min after HCl administration and a third dose two hours after HCl. The animals were then sacrificed, the chest opened, both lungs examined grossly, and sections of affected and unaffected tissue from both lungs obtained for microscopic examination.

e. Endotoxin: Sepsis is one of the most lethal causes for ARDS. Other studies have shown the dog to be resistant to sepsis-related ARDS (21,22). In this study, 6 dogs were given 2.5 mg/kg E. coli endotoxin (Difco) one hour after 10 mCi Tc-HSA. Scintigraphy was continued for three hours in five dogs and five hours in one dog. PAP, PCWP, and SAP were monitored throughout the study period.

D. Results

1. Sheep

a. An attempt was made to scan three sheep while awake and suspended beneath the gamma camera. The animals could not be satisfactorily immobilized to achieve stability of the regions of interest (i.e. lungs and heart).

b. Four sheep were found to have high SI's durng he "control" period following thoracotomy and lymph duct cannulation. The effect of endotoxin administration in these animals could not be interpreted. Two sheep have recently been studied and found to have rising SI's during the control period. The study was aborted and the lungs removed. Gross and histologic examination revealed evidence of a primary pneumonia in both animals.

c. Five sheep were studied prior to and following thoracotomy without lung retractionor lymphatic duct cannulation. Three animals had a high SI during the control period and were deleted from the study. The SI's in the remaining two sheep were 0.7 and 0.1 x 10^{-3} U/min during the control period and 0.3 and 0.5 x 10^{-3} U/min, respectively, following thoracotomy. Little difference was noted in the slopes in these two animals between before and

after thoracotomy. Several more studies are required before this group can be statistically compared to itself or to the next group (See d).

d. Seven sheep were studied prior to and following thoracotomy, lung retraction, and lymphatic duct cannulation. Two animals had a high SI during the control period and were deleted from the study. The mean control SI in the remaining five sheep was $0.6 \pm 0.6 \times 10^{-3}$ U/min. Following thoracotomy, lung retraction and lymphatic duct cannulation, the SI rose significantly ($p<0.01$) to $1.3 \pm 0.6 \times 10^{-3}$ U/min. The acute lymphatic duct cannulation model, therefore, appears to have a significant injury to the lung according to the scintigraphic pulmonary capillary protein leak technique.

2. Dogs

a. Oleic Acid Injury: Of 28 dogs studied, 5 dogs had an SI greater than 0.6×10^{-3} U/min during the control period and were deleted from the study. The following data were obtained:

Study Group	SI ($\times 10^{-3}$ U/min)
Control oleic acid (OA) 0.05 ml/kg	2.9 ± 1.0
Methylprednisolone (30 mg/kg) + OA	3.8 ± 1.9
Ibuprofen (12 mg/kg) + OA	3.8 ± 0.8
MK 447 (4 mg/kg) + OA	2.9 ± 0.3
Ca^{++} Gluconate (140 mg/kg) + OA	3.0 ± 0.4

Therefore, none of the agents tested were able to prevent scintigraphic evidence of an oleic acid pulmonary microvascular injury.

b. Sodium Morrhuate (NaMor): Neither 5 ml nor 20 ml of NaMor produced a significant rise in SI over five hours of study following multiple doses of Tc-HSA. A slight, but transient, rise in PAP was seen following NaMor. There was no change in PCWP. This neutral salt preparation of fatty

acids does not produce pulmonary microvascular injury seen following the free fatty acid, oleic acid.

c. Intralipid: A marked increase in PAP (from 17 ± 4 to 32 ± 6 mmHg) was seen following 500 ml of 20% intralipid with a modest rise in PCWP (from 8 ± 3 to 16 ± 2) in each of the 4 dogs. The serum became grossly lipemic. Nevertheless, no rise in SI was seen over five hours in any animal. One must question any relationship of increased serum neutral fat to ARDS. Similar results have also been noted in a sheep lung lymph cannulation study (24).

d. HCl Studies: Six animals were studied with nebulization of 1.0 N HCl. For reasons that are unclear, no rise in SI was seen in any of these animals. Unfortunately, the lungs were not removed for gross or histologic examination, nor was the pH of the aspirate measured. The reasons for the failure to see any scintigraphic effects are unknown. More recently, 2 dogs were given 2 ml/kg of 0.1 N HCl injected into the trachea with the animal in the right lateral decubitus position. In each case, a markedly positive SI was seen, analogous to that seen with 0.05 ml/kg oleic acid and the SI was reproducible two hours following HCl.

e. Canine Endotoxin Studies: Two of the six dogs studied had a significant SI during the control period and were subsequently deleted from the study. In the four remaining animals, 2.5 mg/kg endotoxin produced an insignificant rise in PAP and PCWP and a marked fall ($p<0.01$) in cardiac output from 3.6 ± 1.24 min to 1.7 ± 0.7 L/min over two hours. An initial small rise in SI was seen in two of these four dogs during the first 60 minutes but was unchanged from control during the second 60 minutes. One animal was studied for four hours and given multiple doses of Tc-HSA without a rise in SI developing. Although more animals need to be studied, there is no scintigraphic evidence

for pulmonary microvascular injury in dogs over two hours following endotoxin. Similar results have been noted by other investigators using different techniques (21,22).

E. Conclusions

A large number of studies has been performed in the first nine months of this contract. The sheep studies showed a significant rise in SI following thoracotomy, lung retraction and lymphatic duct cannulation. Preliminary data suggest that thoracotomy alone does not cause a rise in SI. Therefore, the acute lung lymph cannulation model appears to be associated with a significant pulmonary microvascular injury. Additional studies are required before this can be concluded with certainty. Additional studies will also be necessary with sheep 24 and 48 hours following the lymph cannulation procedure to determine if the injury persists.

A number of sheep had SI's >0.6 during the control period, prior to injury. The cause for this is not clear at this time. Perhaps the sheep were ill and had viral pneumonia. Current plans include chromatography of all Tc-HSA preparations to assure >95% tagging efficiency and early analysis of the control lung:heart radioactivity ratios. If an SI >0.6 is noted, the animal will be sacrificed and the lung removed for gross and histologic examination. Study of two such animals confirmed evidence of pulmonary disease.

Unfortunately, it was not possible to study awake, cannulated sheep beneath the gamma camera. Perhaps a gamma probe system, with one probe over the heart and another over the lung, will permit study of awake animals and, of greater import, will provide "on-line" lung:heart radioactivity ratios.

The dog studies showed that none of the agents tested (methylprednisolone, ibuprofen, MK-447 or calcium gluconate) were able to alter the scintigraphic evidence of oleic acid induced pulmonary microvascular injury when given prior

to the administration of oleic acid. Several studies have suggested that methylprednisolone will prevent oleic acid injury (25,26); whereas, other studies have found no effect on lung water with this medication (27). The data from our study are quite clear that pharmacologic doses of methylpredniso_one had no effect on the pulmonary capillary leak of albumin.

The studies of the effect of sodium morrhuate (NaMor) in dogs demonstrated no scintigraphic evidence of a pulmonary capillary protein leak. No change in pulmonary artery pressures (PAP) were noted in these dogs following NaMor. A study of this agent using the lung lymph technique in sheep performed in another laboratory in our institution demonstrated a marked rise in PAP and an increase in lymph flow with a fall in lymph protein concentration. This agent, therefore, does not appear to cause permeability pulmonary edema in either the sheep or dog. The ARDS seen in patients following sclerotherapy of esophageal varices is, therefore, probably related to aspiration of gastric contents or blood or, perhaps, secondary to a marked increase in PAP.

Massive infusions of intralipid produced grossly lipemic serum and pulmonary artery hypertension but did not cause scintigraphic evidence of a pulmonary capillary protein leak. Perhaps infusions of heparin to activate lipoprotein lipase, or infusion ofthis enzyme itself, mi_ht release free fatty acids which would then produce pulmonary microvascular injury. These studies have not yet been undertaken.

The 0.1 N HCl infusion studies demonstrated a marked rise in SI which persisted over two hours and was analogous to the SI seen with 0.05 ml/kg oleic acid. Severe injury was confirmed by gross and microscopic examination of lung tissue. This model will soon be ready for study of other agents (i.e. methyl-prednisolone, ibuprofen) to ameliorate HCl aspiration injury.

Endotoxin (2.5 mg/kg) produced a significant rise in PAP but did not produce scintigraphic evidence of a pulmonary capillary protein leak over two hours in three dogs and four hours in one dog. Additional studies are necessary before we can conclude with certainty that no injury was seen. However, studies in another laboratory at this institution, using dogs with lung lymph cannulation, demonstrated no evidence of increased pulmonary permeability. This agrees with other published data (21,22).

F. Recommendations

Pulmonary contusion and the acute respiratory distress syndrome were major complications of the Korean conflict, where it was termed the "Traumatic Wet Lung Syndrome," and Viet Nam, where it was called "Da Nang Lung" (29-32). A major cause of death following trauma is sepsis which leads to multi-system organ failure. In a 1977 study by Eiseman et al. (33), 42 patients were found with multiple system organ failure of whom 29 were septic and 19 died. Average hospital costs, excluding physician's fees, were conservatively estimated at $21,000. Fry et a. (34) found that sepsis was the most common cause of multiple system organ failure and this was the most common fatal expression of severe sepsis. Of 553 consecutive emergency surgical patients, 55 died postoperatively. Of these, infection was the cause of death in 32. Thirty-four of 123 septic patients had multiple system organ failure. The lung is the most common organ injured in the septic patient.

There is no currently accepted objective measurement of a pulmonary capillary protein leak that can be used clinically. The thermal-cardiogreen method will purportedly measure the amount of lung water that has already leaked (5-8), but does not determine if an active protein leak is occurring.

The proposed method of computerized pulmonary gamma scintigraphy is conceptually simple, noninvasive, reproducible and should permit the objective evaluation of the presence and duration of ARDS, and its response to therapeutic interventions. Should a treatment be found to be efficacious, the severity of ARDS should be reduced as well as the attendant morbidity associated with the leakage of proteinaceous fluid which is a rich culture medium and the need for prolonged mechanical ventilation. This should improve the resuscitation of the severely injured combat soldier so that he can be returned sooner to active duty or more rapidly rehabilitated.

Additional experiments with the scintigraphic technique are required to complete our sheep acute injury study. However, the results already obtained suggest that data from the acute sheep lung lymph model must be interpreted with caution. Additional studies are necessary to evaluate a chronic sheep model.

A number of sheep and dogs were found to have rising lung:heart radioactivity ratios during the "control" period. These animals have been excluded from further analysis. However, the cause for this finding must be found. Possible etiologies include an incomplete binding of the technetium to the human serum albumin. Unfortunately, chromatographic analyses of the Tc-HSA were not performed in those studies. Subsequently, all preparations of Tc-HSA have been checked and found to have more than 98% binding. It is probable that these animals had a primary pulmonary condition such as a viral pneumonia (i.e., distemper). Therefore, we recommend that lung:heart radioactivity ratios be checked in future studies during the "control period" and, if a "slope of injury" is found, the study should be aborted, the lungs excised and examined for gross and microscopic evidence of disease. Two sheep have recently been studied and were found to have evidence of a viral pneumonia.

Although methylprednisolone, ibuprofen, a superoxide radical scavenger (MK-447), and calcium gluconate were unable to alter oleic acid injury, a number of other agents should be tested. These include prostacyclin (PGI_2), since a recent report suggested it to be effective (28), superoxide dismutase and catalase, and a calcium channel blocker (i.e., nifedipine). In addition, other free fatty acids, such as linoleic and linolenic acid, should be studied. These studies are indicated because of the probable relationship between free fatty acids and the pulmonary fat embolism syndrome of traumatized combat soldiers, as well as ARDS associated with pancreatitis.

Massive doses of intralipid were not associated with scintigraphic evidence of pulmonary capillary protein leak. Because of the relationship of pancreatitis and pulmonary fat embolism to hyperlipidemia and ARDS, one must question whether free fatty acids must be released from the neutral fat before an injury can be seen. We recommend that infusions of intralipid be combined with infusions of heparin, in order to activate lipoprotein lipase, or combined with the intravenous administration of lipase. If scintigraphic evidence of a protein leak is seen, appropriate controls will be required.

We also plan to study the effect of various agents, i.e. methylprednisolone, ibuprofen, etc. on ameliorating the scintigraphic evidence of alveolar injury in the HCl aspiration model. Since endotoxin produced no evidence of a pulmonary capillary protein leak in our scintigraphic studies in dogs, or with bacteria in other studies (21), the dog will no longer be studied as a septic model for ARDS.

In conclusion, computerized pulmonary gamma scintigraphy represents a rapid, noninvasive method for detection and assessment of the severity of a pulmonary capillary protein leak in experimental animals as well as the response to a therapeutic intervention. This should improve over understanding of the pathophysiology, as well as therapy, in combat soldiers who develop ARDS.

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Abstracts and Articles

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1. Sugerman, H.J., Blocker, C.R., Hirsch, J.I., Tatum, J.L., and Strash, A.M.: Failure of methylprednisolone, ibuprofen and MK-447 to alter scintigraphic measurement of oleic acid permeability edema. Circ. Shock 9:197(A), 1982.

2. Sugerman, H.J., Tatum, J.L., Hirsch, J.I., et al.: Gamma scintigraphic measurement of albumin flux in ARDS: A review of the development and validation of the method. J. Clin. Surg. (To be published).

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